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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/904,485
Filing Date: July 13, 2001
Appellant(s): ASHKENAZI ET AL.

Barrie Greene
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 05 August 2005 appealing from the Office action mailed 01 October 2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/944,929 – filed 31 August 2001

10/677,471 – filed 02 October 2003

09/989,729 – filed 19 November 2001

09/993,748 – filed 14 November 2001

09/906,742 – filed 16 July 2001

09/904,011 – filed 11 July 2001

The '742 and '011 applications are directly related to the instant appeal because the claims are directed to polynucleotides encoding PRO217 and antibodies that bind PRO217 polypeptides, respectively and the instant claims are directed to PRO217 polypeptides. The other applications are related to the instant appeal because the central issue of the appeal is whether utility is demonstrated by activity in the MLR (mixed lymphocyte reaction) assay. Because the issue in question is the same, these appeals may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. This list is not exhaustive, but are at least those appeals known to the Examiner in which the central issue of the appeal is the

whether utility is demonstrated by activity in the MLR (mixed lymphocyte reaction) assay.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is essentially correct. However, the conclusion by Appellant at page 4 regarding Example 74 establishing utility for the claimed invention for treatment of conditions where enhancement of an immune response would be beneficial is the subject of the Appeal. Appellant's conclusions should not be part of the Summary of the Claimed Subject Matter.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

- Piccotti et al. Transplantation 67(11) : 1453-1460, 1999.
- Campo et al. Biological Trace Element Research 79 : 15-22, 2001.
- Kahan. Current Opinion in Immunology. 4: 553-560, 1992.
- Manual of Clinical Laboratory Immunology, 6th edition, E. by Rose, Hamilton, Detrick. ASM Press, Washington D.C., 2002.
- Basic and Clinical Immunology, 8th edition, E. by Stites, Terr, Parslow. Appleton and Lange, Norwalk, Connecticut, 1994.
- Hsieh et al. Nature 398: 431-436, 1999.
- Brewer et al. WO 98/54963, December 10, 1998.
- Current Protocols in Immunology, unit 3.12, edited by J. E. Coligan, A. M. Kruisbeek, D. H. Marglies, E. M. Shevach, W. Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (cited by Appellant).
- Fung-Leung et al. Transplantation 60: 362-368, 1995 (cited by Appellant).
- Shim et al. Proc. Natl. Acad. Sci. USA 99(16): 10617-10622, 2002 (cited by Appellant).
- Steinman et al. Drug News Perspect. 13(10): 581-586, 2000.
- Gubler et al. PNAS 88: 4143, 1991 (cited by Appellant).

- Peterson et al. J. Clin. Oncol. 21(12): 2342-2348, 2003 (cited by Appellant).
- Thurner et al. J. Exp. Med. 190(11): 1669-1678, 1999 (cited by Appellant).
- U.S. Pat. No. 5,817,306 HASKILL et al. 10-1998 (newly cited by Examiner).

(9) Grounds of Rejection

The grounds of rejection in the instant application are a direct result of the determination of priority for the claimed subject matter. Appellant asserts priority of the instant application to PCT/US98/19437, filed September 17, 1998. However, priority has not been granted to this earlier application.

According to the priority statement of 26 August 2002, it appears that the claimed subject matter (PRO 217) defined in the instant application is supported by PCT application PCT/US00/04414 filed 2/22/2000. Based on the invention given by Appellant and an inspection of the patent applications, the Examiner has concluded that the subject matter defined in this application is supported by the disclosure PCT//US00/04414, filed 2/22/2000 but is not supported by any of the other applications because the claimed subject matter does not have utility/enablement for the asserted utility of those applications (i.e. asserted utility of stimulating the immune system). The use of the claimed invention for inhibition of VEGF stimulated proliferation of adrenal cortical capillary endothelial cells is first taught in PCT/US00/04414, and this is found to

have utility and is enabled by the specification as tiled. However, PCT/US98/19437, filed 9/17/1998 does not teach this utility, and therefore, priority is not granted to this application.

First, it should be made clear that the claimed invention has met the utility requirement based on its activity of inhibiting VEGF stimulated proliferation of adrenal cortical capillary endothelial cells. However, the asserted utility that the claimed invention could be used therapeutically to enhance the immune response in an individual does not meet the requirements of 35 U.S.C. § 101. The instant specification discloses that the claimed protein (PRO217 – SEQ ID NO:4) tested positive in the MLR assay wherein **"positive increases over control are considered positive"** (see pages 208-209 of the specification).

It was previously asserted by the Examiner that insufficient evidence was provided to support the position that the MLR assay was an art recognized *in vitro* assay that was predictive of general immune responses *in vivo*. Several references were cited during the prosecution of the instant application which demonstrated either a showing that the results of the MLR assay were consistent with *in vivo* activity or were inconsistent with *in vivo* activity. Upon review of the prior art, the Examiner found a patent that states "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. The results obtained from these assays are generally predictive of their *in vivo* effectiveness." (See column 12, lines 36-41 of U.S. Pat. No. 5,817,306). Therefore, it is conceded that the MLR assay is art

recognized for identifying molecules which suppress an immune response. It would also be likely that the assay would be useful for identifying molecules which stimulate an immune response.

However, the instant specification does not support a utility for the claimed invention for the asserted use of enhancing the immune response in an individual based on the results of the MLR assay in Example 74 (page 208-209 of the specification). The specification at page 209, lines 17-18, states "Positive increases over control are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein." The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that certain proteins tested positive and the statement that **"any value greater than control indicates a stimulatory effect for the test protein".**

If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth regarding the nature of the MLR assay and how those skilled in the art use this assay and what kind of determinations can be made about compounds which are tested in this assay. The MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay.

Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. The art recognizes several controls as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities (Basic & Clinical Immunology, page 246). Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion of the specification. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because one of ordinary skill in the art would not conclude that a molecule

which tested positive in the assay of the specification wherein "positive increases over control are considered positive" would be useful as a molecule for therapeutically enhancing an immune response in an individual (asserted use). There is insufficient data presented, as well as insufficient controls used, to conclude anything regarding the ability of the claimed invention to be used in a substantial way to therapeutically enhance the immune response of an individual, and further experimentation would be required to use the invention in this manner.

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC §112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-43, 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:4 or the mature form thereof, which isolated polypeptide inhibits VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, does not reasonably provide enablement for a polypeptide not identical to at least the mature form of SEQ ID NO:4 which is capable of stimulating proliferation of T-lymphocytes.

The claims include the limitation that "the polypeptide encoded by said nucleic acid is capable of stimulating proliferation of T-lymphocytes". The basis for this limitation is found in Example 74, which has been shown not to support utility for the claimed invention, and therefore, is likewise, not enabled. (See above under Priority). Example 74 of the specification is stimulatory activity in a mixed lymphocyte reaction (MLR). However, this disclosure is not sufficient to conclude that the claimed protein has the ability to stimulate lymphocyte proliferation because the condition for concluding that the protein tested positive is "**any value greater than control indicates a stimulatory effect for the test protein".** The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary sill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that "positive increases over control are considered positive", however, this does not

indicate that statistical significance must occur for determination of a positive result in the assay. For these reasons it would require undue experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

Claims 39-43 are rejected under 35 U.S.C. 102(a) as being anticipated by HSIEH et al. (Nature 398: 431-436, 1999).

HSIEH et al. disclose an isolated polypeptide which has 99.7% amino acid sequence identity to the amino acid sequence of the polypeptide shown in Figure 4 (SEQ ID NO:4). See Figure 1 . HSIEH et al. further disclose a chimeric molecule. including a fusion with an IgG heavy-chain ('see paragraph 7). Therefore, the claims are anticipated by the prior art.

Claims 44-45, 49 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over HSIEH et al. (Nature 398: 431-436, 1999).

The disclosure of HSIEH et al. is as described above. The single difference in amino acid sequence between the polypeptide of SEQ ID NO:4 recited in the instant claims and the polypeptide of HSIEH et al. occurs at position 178. Specifically, the amino acid at position 178 in SEQ ID NO:4 of the instant application is glutamine, whereas the amino acid at position 178 of HSIEH et al. is leucine. The courts have long recognized that sequencing errors can occur (*Ex parte Maizel*; 27 USPQ2d 1662, BPAI 1992, see especially pp. 1663 and 1666). The instant specification also recognizes that

the sequences disclosed in the sequence listing may not be exact. At page 157 of the instant specification, it is stated that

> "for the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time."

Therefore, it is reasonable to expect that the single amino acid difference at position 178 of SEQ ID NO:4 of the instant application and the protein of HSIEH et al. may be the result of a sequencing error, and that the actual clones of the instant application and HSIEH et al., in fact, have identical sequences.

The Examiner is unable to determine whether the prior art disclosure actually possesses the characteristic of the sequence of SEQ ID NO:4. With these conditions, where the product seems to be identical, then the burden shifts to Appellant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

Claims 39-43 are rejected under 35 U.S.C. 102(b) as being anticipated by BREWER et al. (WO 98/54963; published 10 December 1998).

BREWER et al. teach a polypeptide (SEQ ID NO:426) which has approximately 99% amino acid sequence identity with the claimed polypeptide of SEQ ID NO:4. (The reference is 772 pages in length, and therefore, the entire document is not provided.) BREWER et al. further disclose a chimeric molecule, including a fusion with an IgG heavy-chain (see page 236). Therefore, the claims are anticipated by the prior art of BREWER et al.

Claims 44-45, 49 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over BREWER et al. (WO 98/54963; published 10 December 1998).

BREWER et al. teach a polypeptide (SEQ ID NO:426) which has approximately 99% amino acid sequence identity with the claimed polypeptide of SEQ ID NO:4 (pages 579-580). The differences between the claimed polypeptide and the polypeptide of BREWER et al. are found at positions 264, 300 and 380. Positions 264 and 300 are indicated to be Xaa. which is a wildcard amino acid. Frequently in the biotech. arts, amino acid sequence analysis fails to reliably provide each and every amino acid in a protein sequence. This is sometimes due to disulfide bonds between cysteine residues.

Therefore, the amino acids at these positions may very well be cysteine residues (inherent to the polypeptide of BREWER et a1), which would anticipate the instant claims since the residues at these positions in SEQ ID NO:4 are cysteine residues. With regard to inherency, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima.facie* case of either anticipation or obviousness has been established. *In re Best*, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 15 USPQ2d 1655, I 658 (Fed. Cir. I 990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 195 USPQ 430, 433 (CCPA

1977). *In re Papesch*, 315 F.2d 381, 137 USPQ 42, 51 (CCPA 1963) held that "From the standpoint of patent law, a compound and all its properties are inseparable."

In the alternative, it would have been *prima facie* obvious for one of ordinary skill in the art to place any one of the known amino acids in the recited positions of BREWER et al. since these positions were indicated to be Xaa, which could be any amino acid. The number of embodiments is relatively small, considering only two positions are indicated and it would be well within the skill of the artisan to substitute these two positions and isolate the encoded protein. It is noted that the protein of BREWER et al. has an extra amino acid at position 380, however, the instant claims recite "comprising", which encompasses additional amino acids.

(10) Response to Argument

Appellant argues, beginning at page 5 of the response, that the MLR is a well-established assay for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro* and that compounds identified by this assay would be useful for enhancing an immune response *in vivo*. As stated earlier, the disclosure of newly cited U.S. Pat. No. 5,817,306 establishes the state of the art at the time the invention was made that the results of the MLR assay are generally predictive of *in vivo* effects. Therefore, arguments directed to the correlation or predictive nature of the MLR assay are moot and will not be addressed further. However, arguments directed toward the disclosure of the specification and conclusion that can be made from such a disclosure will be addressed since they are critical to the holding of denial of priority

based on lack of utility for stimulation of T-lymphocyte proliferation by the claimed invention.

Appellant states at page 5 of the response that the Declaration of Dr. Sherman Fong was submitted July 12, 2004. This declaration has been fully considered, but not found to be persuasive. Dr. Fong concludes "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant". In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Develonment Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not the disclosure that PRO217 tested "positive" in the MLR assay of Example 74 supports the assertion that it could be used to stimulate proliferation of T-lymphocytes and therefore, be used for therapeutic enhancement of the immune system. Dr. Fong's statement that the present invention has an activity of at least 180% is questioned because there is no data presented to support this conclusion. The specification may state that increases of greater than or equal to 180% are preferred, but there is no

disclosure, in the specification or in any other source, that the alleged increase reported in the specification for the claimed protein was of any particular degree. The only conclusion that can be made from the evidence provided for the claimed protein of PRO217 is that the increase was a value greater than control since this was the standard provided for determination of a positive increase. The significance of this conclusion can be questioned since proper assay controls, deemed essential in the art, were not used and because the standard for determination of a positive response in the assay would not be accepted by those of skill in the art (statistical significance is the standard for evaluating therapeutic value of a compound). The expert has interest in the outcome of the case since Dr. Fong is listed as an inventor and is employed by the assignee. Finally, the expert refers to Gubler et al. as factual support for the conclusions in the declaration. However, Gubler et al. do not appear to indicate that a protein shown to stimulate T-cell proliferation in an MLR assay with an activity of at least 180% would be expected to have the type of activity as that exhibited by IL-12. Furthmore, Gubler et al. (as well as Peterson et al. and Thurner et al.) are silent to any activity possessed by the claimed protein. The Fong declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO217 protein has not been shown to therapeutically enhance the immune system. The specification merely demonstrates that the PRO217 protein increases T-cell proliferation above control. It is not known whether this increase is significant or what the relative increase in proliferation is. In the absence of any of the above information, all that the specification does is present evidence that the PRO217 protein

may increase T-cell proliferation and invites the artisan to determine the significance of this increase and whether it is meaningful (i.e. useful for a therapeutic benefit). It remains that the specification is not sufficient to conclude anything about the nature of the activity of the PRO217 protein. Based on consideration of the evidence as a whole, the finding of lack of utility based on the MLR assay of Example 74 is proper.

Appellant argues at page 6 of the Brief that the standard for utility is that it is "more likely than not" that the asserted utility is specific and substantial and that the Examiner "has misinterpreted the focus of the assay disclosed in the specification". Appellant's argument has been fully considered, but is not persuasive. The question of whether the art recognizes the MLR assay as predictive of *in vivo* therapeutic value has been answered. However, the specification does not support the conclusion that the claimed protein (PRO217) stimulates proliferation of T-lymphocytes such that it would have therapeutic application for enhancing the immune response. As pointed out previously, no data is presented and the statement that proliferation was greater than control is not sufficient for concluding that the claimed protein would be useful for a therapeutic application, which is the asserted utility based on this assay. The assay relied upon in the instant specification is deficient in that proper art-recognized controls are not present, measured values of stimulation are not present, variability is not disclosed, statistical significance is not disclosed, such that an independent evaluation and conclusion cannot be made. One skilled in the art would have to do further research to determine whether or not the increase in T-cell proliferation by PRO217 polypeptide in the MLR assay is real and significant, and therefore, support the asserted

use for therapeutic enhancement of immune response. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

At page 7 of the Brief, Appellant's arguments regarding enablement appear to depend from the arguments regarding use of the claimed protein for stimulating an immune response. These arguments have been addressed above, and therefore, do not require repeating.

Appellant argues at page 8 of the Brief that the instant application claims priority to an earlier filed application (60/100,858, filed September 17, 1998) and that they are entitled to benefit to this earlier filed application based on the disclose that PRO217 tested positive in the MLR assay. As pointed out in the grounds of the rejection, this is an issue to be addressed in this Appeal. If the disclosure in the specification is deemed sufficient to provide utility for the claimed invention based on the asserted use for therapeutic stimulation of an immune response, then Appellant is entitled to the effective

filing date of the 60/100,858 application. However, priority has been denied because the disclosure has been found insufficient to establish this utility for the claimed invention.

At pages 9-11, Appellant reviews case law pertaining to the legal standard for patentable utility, with which the Examiner does not take issue. At page 12, Appellant asserts that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. MPEP § 2170.01 also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." In the instant situation, further research would be required to reasonably confirm that the claimed protein stimulates T-cell proliferation to a degree that it would be useful therapeutically for stimulating an immune response, which is the asserted utility in the specification.

Appellant states at page 12 of the Brief "[t]he positive result for PRO217 in the MLR assay, described in Example 74, at pages 208-209 of the specification, demonstrates that PRO217 is active as a stimulator of the proliferation of stimulated T-lymphocytes". Appellant's assertion is noted, but the facts of record and the disclosure of the specification do not support this conclusion. As pointed out previously, the specification indicates that "positive increases over control are considered positive", yet

art recognized controls, which are considered to be necessary for determining a meaningful result, are not present. The specification fails to include any values which were obtained from the assay, so the results of the assay cannot be independently evaluated. If the degree of stimulation is greater than the control, but within the variability of the assay, then one of ordinary skill in the art would not conclude that the protein tested is a stimulator of T-cell proliferation, yet the specification would arrive at this conclusion. In order to be useful in the manner asserted in the specification (i.e. therapeutic enhancement of an immune response), the degree of stimulation of T-cell proliferation must be meaningful. One of ordinary skill in the art would usually evaluate this by observing a statistically significant increase in T-cell proliferation over baseline. However, based on the limited disclosure in the instant specification, no conclusions can be made as to the activity of the claimed protein in this assay because proper controls are not provided and there is no data presented to evaluate. Therefore, further research would be required to reasonably confirm the asserted utility based on the MLR assay of Example 74.

Appellant's statements and arguments (pages 12-14) directed to use of the MLR to evaluate compounds for use as immunomodulators is noted. However, in view of the Examiner's concession that the MLR is an art accepted assay for this purpose, these arguments are moot.

Appellant again refers to the Declaration of Dr. Fong at page 15 of the Brief. As stated previously, the Declaration has been fully considered but is not persuasive. Appellant asserts that the "specification clearly discloses that PRO217 tested positive in

the MLR assay" and that the "Fong Declaration reinforces the teachings of the specification that a PRO polypeptide with an activity in the MLR assay of at least 180% of the control is expected to have the type of activity exhibited by IL-12, and would therefore find practical utility as an immune stimulant" (see page 16 of the Brief).

First, the statement that PRO217 tested positive in the MLR assay is addressed above. The standard set forth in the specification that "positive increases over control are considered positive" is neither art accepted nor indicative of a meaningful increase in T-cell proliferation. Lacking proper controls and no data, the observation that PRO217 tested "positive" is meaningless. All assays have variability and the observed increase over control may be natural variation in the assay, and therefore, not an indication of an immunostimulatory effect. Secondly, there is no disclosure that the PRO217 protein of the instant invention has an activity in the MLR assay of at least 180%, therefore, no conclusions regarding it's activity can be made and one would not conclude that it would have practical utility as an immune stimulant. The Declaration of Dr. Fong is not specific to the claimed protein, PRO217. The Declaration provides no data related to the claimed protein, PRO217. Furthermore, the opinion of Dr. Fong that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12" is not supported by any facts or evidence of record. The references cited do not support this opinion and it is not clear how Dr. Fong arrived at this conclusion. There is no evidence of record which correlates an activity of at least 180% of control as predictive of an activity of IL-12 and there is no comparison

of the claimed invention with IL-12. One of ordinary skill in the art would not conclude that the claimed protein has the activity of IL-12 because there is absolutely no data provided to support such an assertion. Therefore, the Declaration is not persuasive to overcome the holding of a lack of utility for the claimed invention based on the MLR assay.

Appellant's arguments spanning page 17-26 are directed to use of the MLR to evaluate compounds for use as immunomodulators is noted. However, in view of the Examiner's concession that the MLR is an art accepted assay for this purpose, these arguments are moot.

Appellant cites case law concerning the Examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be considered. Appellant also points to the utility guidelines as directing the Examiner to accept an opinion from an expert. Appellant points to the statement in the Fong declaration that it is Dr. Fong's considered scientific opinion that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant". Appellant concludes that "barring evidence to the contrary regarding the above statement in the Fong declaration, this rejection is improper under both the case law and the Utility guidelines". This has been fully considered but is not found to be persuasive.

As discussed above, in assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought

to be established (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not Example 74 of the specification demonstrates that the claimed invention, PRO217, would be useful for therapeutic enhancement of an immune response. (2) The art provides support that the results of the MLR assay are generally predictive of *in vivo* effects (Haskill et al.), but the art also teaches that proper controls are required for meaningful results. These controls appear to be lacking in the instant application. Additionally, the standard used in the specification (positive increases above control are considered positive) would not be accepted by those in the art as indicating that the claimed invention would have therapeutic value for enhancing an immune response. The art to which the invention pertains is immunology and the art accepted standard for determining biological activity is statistical significance. Since no values are provided, statistical significance cannot be ascertained. (3) Dr. Fong has an interest in the case since he is employed by the assignee. Finally, (4) while Dr. Fong bases his findings with reference to facts, the conclusions arrived at are not supported by those facts. For example, there is no evidence that the protein claimed, PRO217, has an activity of at least 180% in the MLR assay. Additionally, the references reviewed by Dr. Fong (Guber et al., Peterson et al., and Thurner et al.) are directed to IL-12, and not to the PRO217 of the instant application. None of the references indicate that an activity of at least 180% in an MLR is indicative of a protein having the type of activity as that exhibited by IL-12. In fact, none of the references use the results of the MLR for IL-

12 to make predictions about the biological activities of any other compounds. The asserted correlation of an activity of at least 180% in an MLR with the biological activity of IL-12 is not supported by any evidence of record, and appears to be the opinion of Dr. Fong. Based on the totality of the evidence, considering it anew, it is maintained that one skilled in the art would view the MLR assay of Example 74 as merely preliminary with regard to whether or not PRO217 would be useful for therapeutic enhancement of an immune response. Further research would have to be done in order to determine if PRO217 stimulates proliferation of T-lymphocytes and, if so, whether or not the stimulation is significant enough to reasonably confirm the usefulness of PRO217 protein for therapeutic enhancement of an immune response. Thus, the specification does not provide products or services in "currently available" to the public, and the asserted utility is not substantial. Because Example 74 (MLR assay) does not support a substantial utility, the applications relied upon for priority based on this Example likewise do not support a substantial utility. The instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because the instant application does not meet the requirements of 35 U.S.C. § 112, first paragraph, for those reasons given above, the prior applications do not meet those requirements and, therefore, are unavailable under 35 U.S.C. § 120 or § 119(e).

Again, the claims were not rejected for lack of utility because a specific, substantial and credible utility was found based on the ability to inhibit VEGF stimulated

proliferation of adrenal cortical capillary endothelial cells (first disclosed in PCT/US00/04414). Therefore, the effective filing date of the instant application is the filing date of PCT/US00/04414 (02/22/2000).

Appellant argues at page 27 of the Brief that the claims are enabled for the same reasons as provided for utility. However, since the arguments were not persuasive for supporting utility, they are also not persuasive for supporting enablement. Because the claimed invention does not have utility for therapeutic enhancement of an immune response, and because the specification does not support the conclusion that PRO217 stimulates T-lymphocytes based on an unreasonable standard for assessing activity and lack of proper experimental controls, the claims are also not enabled for protein variants that stimulate proliferation of T-lymphocytes.

Appellant argues that one skilled in the art could test whether a variant PRO217 polypeptide is capable of stimulating proliferation of T-lymphocytes. This argument has been considered but it is not persuasive. The specification has not provided sufficient evidence to support the assertion that the claimed invention is capable of stimulating proliferation of T-lymphocytes. Therefore, the claimed invention does not have utility for stimulating proliferation of T-lymphocytes for the reasons provided above, and likewise, the claims are not enabled for this use. If the PRO217 protein is not enabled, the variants as well are not enabled. The rejection was made as a scope rejection, because the PRO217 protein does have utility and enablement for it's ability to inhibit VEGF stimulated proliferation of adrenal cortical capillary endothelial cells.

Appellant argues the rejection of the claims based on the prior art of Hsieh et al. and Brewer et al. at pages 29-31. Essentially, Appellant contends that priority to provisional application 60/100,858 should be granted because the MLR assay was first disclosed in this application, and the MLR assay supports utility and meets the requirements of 35 U.S.C. 112 for the subject matter of the instant claims. However, because the arguments regarding utility based on this assay were not persuasive for the reasons provided above, the instant application is not entitled to benefit of this earlier filed application. Therefore, the effective filing date is the filing date of PCT/US00/04414, filed 2/22/2000, which discloses the ability of PRO217 to inhibit VEGF stimulated proliferation of adrenal cortical capillary endothelial cells. Therefore, the rejections based on Hsieh et al. and Brewer et al. are maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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